REMARKS

Entry of this amendment and favorable reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-99 are in this case. Claims 21-50 and 71-99 were withdrawn under a restriction requirement as drawn to a non-elected invention. Claims 1-20 and 51-70 have been rejected. Claims 1 and 51 have now been amended.

35 U.S.C. § 103(a) Rejections

The Examiner has rejected claims 1-20 and 51-70 under 35 U.S.C. § 103(a) as being unpatentable over Naughton et al. in view of Sussman et al. and Stephanopouos et al. Claims 1 and 51 have now been amended.

The Examiner states that Naughton et al., disclose the growth of bone marrow stromal cells on a three dimensional matrix, which can be formed from a polymeric material, followed by the inoculation of the stromal matrix with stem cells and maintenance of the stem cells in vitro where proliferation of the cells is maximized to thereby allow long-term maintenance of hematopoietic cells.

The Examiner further states that Sussman et al. disclose a fibrous matrix for cell cultivation. The matrix can be a non-woven fiber sheet with distinct pore volume, pore size and height, which can be used as a packing in a column and coated with poly-D-lysine.

The Examiner further states that Stephanopolous et al. disclose a cell-culturing reactor having an inlet and outlet for culture medium and containing a macroporous support between the inlet and outlet having pores of a size that allows cells to collect within the pores and oxygen and nutrients to migrate into the pores for consumption by the cells.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time of the invention was made to use the matrix of Naughton et al. and the non woven fibrous sheet packed in a column for cell-culture disclosed by Sussman et al. to obtain a flow through reactor having an inlet and outlet as suggested by Sussman et al. and Stephanopoulos et al. since such a reactor would

have been expected to provide culturing advantages.

The Examiner states that Naughton et al. do not disclose the differentiation state of the cells prior to implanting. The Examiner further states that the claimed invention does not require conditions unobviously different from Naughton et al. that would maintain the cells differentiationless.

Notwithstanding the above, and in the interest of expediting prosecution of this application, Applicant has elected to add claim limitations, which in the opinion of the Applicant, to more clearly distinguish the present invention from the prior art cited.

Thus, claim 1 has been amended to recite the following:

> A method of expanding/maintaining undifferentiated hemopoietic stem cells or progenitor cells, the method comprising the steps of:
>
> (a) culturing a three dimensional stromal cell culture under medium flow conditions in a stationary phase plug-flow bioreactor on a substrate in the form of a sheet, said substrate including a non-woven fibrous matrix forming a physiologically acceptable three-dimensional network of fibers; and
>
> (b) seeding the undifferentiated hemopoietic stem cells or progenitor cells into said stationary phase plug-flow bioreactor thereby expanding/maintaining the undifferentiated hemopoietic stem cells or progenitor cells. (Emphasis added)

Amended claim 51 also recites similar limitations.

The instant application suggests that growing high-density 3-D stromal culture requires a continuous flow of growth media through 3-D cell carriers settled within the plug-flow bioreactor. The rationale being that a flow system allows the

passage of oxygen and nutrients to the cells and removal of waste materials from the cells through an active transfer rather than by diffusion.

The present invention anticipates that stromal 3-D cultures grown in a static system, similarly to the system described by Naughton and co-workers, cannot reach a sufficient density to support the survival and expansion of hematopoietic stem cells and progenitor cells, which is the essence of the present invention.

The advantage of the culturing method of the present invention over "static" culturing approaches is discussed by the instant application, see, for example the text on page 17 lines 16-22 which states the following:

> "The bioreactor described herein is unique in that it combines both 3D stromal cell cultures with a continuous flow system. While 3D stromal-hemopoietic cell systems without continuous medium flow have recently been described (U.S. Pat. No. 5,541,107), the findings described herein (see, for example, Figure 7) clearly demonstrate the diminished advantage of 3D stromal cell cultures relative to monolayers, in the absence of continuous flow." (Emphasis added)

To further emphasize the advantages of the present invention over prior art culturing methods, Applicant has applied the culturing conditions set forth in the instant application and in the teachings disclosed by Naughton and co-workers to hemoatopoietic stem cells (HSCs) and progenitor cells cultures. The results of this study (reported in the enclosed Appendix) which were obtained following filing of the instant application, demonstrate the superior ability of 3-D stromal cultures which are grown in the presence of continuous medium flow to support growth of hemoatopoietic stem cells (HSCs) and progenitor cells, as compared to the static conditions described by Naughton and his co-workers.

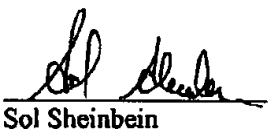
The study showed that growth of hematopoietic stem cells (CD34+, Figure 1a) and earlier progenitors (CD34+38-, CD34+38-CXCR4+, Figures 1b and 1c, respectively) was at least 3 fold better in the presence of stromal cultures which were grown in the presence of continuous medium flow (see the "bioreactor total" bar of Figures 1a-c) as compared to the static conditions described by Naughton and

co-workers (see the "carrier + stroma" bar of Figures 1a-c).

Thus, it is Applicants strong opinion that flow conditions and 3-D carriers are essential for the maximal growth of stromal cell cultures, which in turn can support the growth and expansion of hematopoietic stem cells and progenitor cells far better than the conditions described by Naughton and his co-workers.

In view of the above amendments and remarks, it is respectfully submitted that claims 1-20 and 51-70 are now in condition for allowance. An early Notice of Allowance is respectfully and earnestly solicited.

Respectfully submitted,



Sol Sheinbein
Registration No. 25,457

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Enc.
Appendix
Declaration by Dr. Shai Meretski